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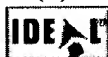
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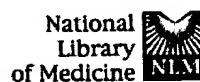
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DSCAM, a conserved gene involved in neuronal differentiation, is a member of the Ig superfamily of cell adhesion molecules. Herein, we report the functional characterization of a human DSCAM (Down syndrome cell adhesion molecule) paralogue, DSCAML1, located on chromosome 11q23. The deduced DSCAML1 protein contains 10 Ig domains, six fibronectin-III domains, and an intracellular domain, all of which are structurally identical to DSCAM. When compared to DSCAM, DSCAML1 protein showed 64% identity to the extracellular domain and 45% identity to the cytoplasmic domain. In the mouse brain, DSCAML1 is predominantly expressed in Purkinje cells of the cerebellum, granule cells of the dentate gyrus, and in neurons of the cerebral cortex and olfactory bulb. Biochemical and immunofluorescence analyses indicated that DSCAML1 is a cell surface molecule that targets axonal features in differentiated PC12 cells. DSCAML1 exhibits homophilic binding activity that does not require divalent cations. Based on its structural and functional properties and similarities to DSCAM, we suggest that DSCAML1 may be involved in formation and maintenance of neural networks. The chromosomal locus for DSCAML1 makes it an ideal candidate for neuronal disorders (such as Gilles de la Tourette and Jacobsen syndromes) that have been mapped on 11q23. Copyright 2001 Academic Press.

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Full Text

**Down syndrome cell adhesion molecule is conserved in mouse and highly expressed in the adult mouse brain.****Barlow GM, Micales B, Lyons GE, Korenberg JR.**

Department of Medical Genetics, Cedars-Sinai Medical Center and UCLA, 90048, USA.

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Down Syndrome (DS) is a major cause of mental retardation and is associated with characteristic well-defined although subtle brain abnormalities, many of which arise after birth, with particular defects in the cortex, hippocampus and cerebellum. The neural cell adhesion molecule DSCAM (Down syndrome cell adhesion molecule) maps to 21q22.2-->q22.3, a region associated with DS mental retardation, and is expressed largely in the neurons of the central and peripheral nervous systems during development. In order to evaluate the contribution of DSCAM to postnatal morphogenetic and cognitive processes, we have analyzed the expression of the mouse DSCAM homolog, Dscam, in the adult mouse brain from 1 through 21 months of age. We have found that Dscam is widely expressed in the brain throughout adult life, with strongest levels in the cortex, the mitral and granular layers of the olfactory bulb, the granule cells of the dentate gyrus and the pyramidal cells of the CA1, CA2 and CA3 regions, the ventroposterior lateral nuclei of the thalamus, and in the Purkinje cells of the cerebellum. Dscam is also expressed ventrally in the adult spinal cord. Given the homology of DSCAM to cell adhesion molecules involved in development and synaptic plasticity, and its demonstrated role in axon guidance, we propose that DSCAM overexpression contributes not only to the structural defects seen in these regions of the DS brain, but also to the defects of learning and memory seen in adults with DS. Copyright 2002 S. Karger AG, Basel

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**DSCAM: a novel member of the immunoglobulin superfamily maps in a Down syndrome region and is involved in the development of the nervous system.**

**Yamakawa K, Huot YK, Haendelt MA, Hubert R, Chen XN, Lyons GE, Korenberg JR.**

Division of Medical Genetics, Cedars-Sinai Research Institute/UCLA, Los Angeles, CA 90048-1869, USA.

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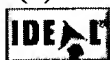
Down syndrome (DS), a major cause of mental retardation, is characterized by subtle abnormalities of cortical neuroanatomy, neurochemistry and function. Recent work has shown that chromosome band 21q22 is critical for many of the neurological phenotypes of DS. A gene, DSCAM (Down syndrome cell adhesion molecule), has now been isolated from chromosome band 21q22.2-22.3. Homology searches indicate that the putative DSCAM protein is a novel member of the immunoglobulin (Ig) superfamily that represents a new class of neural cell adhesion molecules. The sequence of cDNAs indicates alternative splicing and predicts two protein isoforms, both containing 10 Ig-C2 domains, with nine at the N-terminus and the tenth located between domains 4 and 5 of the following array of six fibronectin III domains, with or without the following transmembrane and intracellular domains. Northern analyses reveals the transcripts of 9.7, 8.5 and 7.6 kb primarily in brain. These transcripts are differentially expressed in substructures of the adult brain. Tissue in situ hybridization analyses of a mouse homolog of the DSCAM gene revealed broad expression within the nervous system at the time of neuronal differentiation in the neural tube, cortex, hippocampus, medulla, spinal cord and most neural crest-derived tissues. Given its location on chromosome 21, its specific expression in the central nervous system and neural crest, and the homologies to molecules involved in neural migration, differentiation, and synaptic function, we propose that DSCAM is involved in neural differentiation and contributes to the central and peripheral nervous system defects in DS.

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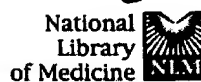
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Down Syndrome Cell Adhesion molecule (DSCAM) is a member of the immunoglobulin superfamily, and represents a novel class of neuronal cell adhesion molecules. In order to understand the cellular functions of DSCAM, we isolated full-length mouse and human cDNA clones, and analysed its expression during mouse development and differentiation. Sequence analysis of the human DSCAM cDNA predicted at least 33 exons that are distributed over 840 kb. When compared to human DSCAM, the mouse homologue showed 90 and 98% identity at the nucleotide and amino acid levels, respectively. In mouse, DSCAM is located on 16C, the syntenic region for human chromosome band 21q22 and also the region duplicated in mouse DS models. DSCAM gene is predicted to encode an approximately 220-kDa protein, and its expression shows dynamic changes that correlate with neuronal differentiation during mouse development. Our results suggest that DSCAM may play critical roles in the formation and maintenance of specific neuronal networks in brain. Copyright 2001 Academic Press.

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## Down syndrome cell adhesion molecule DSCAM mediates homophilic intercellular adhesion.

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Services**Agarwala KL, Nakamura S, Tsutsumi Y, Yamakawa K.**

Laboratory for Neurogenetics, Brain Science Institute, Institute of Physical and Chemical Research (RIKEN), Saitama, Japan.

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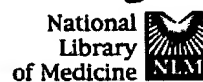
Down Syndrome (DS) caused by trisomy 21 is the most common birth defect associated with mental retardation. Recently, a novel gene named, DSCAM, has been identified in the DS critical region. DSCAM is predicted to be a transmembrane protein with a very high structural and sequence homology to Ig superfamily of cell adhesion molecules and is expressed in the developing nervous system with the highest level in fetal brain. Diverse glycoproteins of cell surfaces and extracellular matrices operationally termed as 'adhesion molecule' are important in the specification of cell interactions during development, maintenance and regeneration of the nervous system. To understand the cellular function of DSCAM protein, we transfected human DSCAM cDNA into mouse fibroblast L cells and analysed its expression. On Western blot analysis, antibodies raised against recombinant DSCAM-Ig3 recognized a 198 kDa protein band in the membrane fraction of DSCAM transfected L cells. Stable transformants expressing DSCAM showed uniform surface expression. DSCAM-expressing transfectants exhibited enhanced adhesive properties, aggregating with faster kinetics and forming aggregates in a homophilic manner. Divalent cations are not required for this cell aggregation. These results demonstrate that DSCAM is a cell adhesion molecule that can mediate cation-independent homophilic binding activity between DSCAM expressing cells.

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### The developmental and aging changes of Down's syndrome cell adhesion molecule expression in normal and Down's syndrome brains.

Saito Y, Oka A, Mizuguchi M, Motonaga K, Mori Y, Becker LE, Arima K, Miyauchi J, Takashima S.

Department of Clinical Laboratory, National Center Hospital for Mental, Nervous and Muscular Disorders, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan.

We studied the expression of Down's syndrome cell adhesion molecule (DSCAM) in Down's syndrome (DS) and control brains, using antisera against peptide fragments of DSCAM. On Western blots of human, mouse and rat brain homogenates, the antisera recognized a product at approximately 200 kDa. In the brain of a 2-year-old patient with DS, Western blotting revealed an overexpression of DSCAM compared to an age-matched control. Immunohistochemistry demonstrated DSCAM in the cerebral and cerebellar white matter of both control and DS subjects, in accordance with the temporal and spatial sequence of myelination. In DS brains, immunoreactivity for DSCAM, compared to that for controls, was enhanced in the Purkinje cells at all ages, and in the cortical neurons during adulthood. In demented DS patients, DSCAM immunoreactivity was observed in the core and periphery of senile plaques. The pattern of DSCAM expression suggests that it may play a role as an adhesion molecule regulating myelination. The overexpression of DSCAM may also play a role in the mental retardation and the precocious dementia of DS patients, although the mechanism of neuronal dysfunction is undetermined.

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Revised: October 24, 2001.

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BLink, Nucleotide, Related Sequences, PubMed,  
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LOCUS NP\_001380 2012 aa linear PRI 10-APR-2002

DEFINITION Down syndrome cell adhesion molecule; human CHD2-52 down syndrome  
cell adhesion molecule [Homo sapiens].

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KEYWORDS .

SOURCE human.

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Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.

REFERENCE 1 (residues 1 to 2012)

AUTHORS Yamakawa,K., Huot,Y.K., Haendelt,M.A., Hubert,R., Chen,X.N.,  
Lyons,G.E. and Korenberg,J.R.

TITLE DSCAM: a novel member of the immunoglobulin superfamily maps in a  
Down syndrome region and is involved in the development of the  
nervous system

JOURNAL Hum. Mol. Genet. 7 (2), 227-237 (1998)

MEDLINE [98087574](#)

PUBMED [9426258](#)

REFERENCE 2 (residues 1 to 2012)

AUTHORS Hattori,M., Fujiyama,A., Taylor,T.D., Watanabe,H., Yada,T.,  
Park,H.S., Toyoda,A., Ishii,K., Totoki,Y., Choi,D.K., Soeda,E.,  
Ohki,M., Takagi,T., Sakaki,Y., Taudien,S., Blechschmidt,K.,  
Polley,A., Menzel,U., Delabar,J., Kumpf,K., Lehmann,R.,  
Patterson,D., Reichwald,K., Rump,A., Schillhabel,M., Schudy,A.,  
Zimmermann,W., Rosenthal,A., Kudoh,J., Schibuya,K., Kawasaki,K.,  
Asakawa,S., Shintani,A., Sasaki,T., Nagamine,K., Mitsuyama,S.,  
Antonarakis,S.E., Minoshima,S., Shimizu,N., Nordsiek,G.,  
Hornischer,K., Brant,P., Scharfe,M., Schon,O., Desario,A.,  
Reichelt,J., Kauer,G., Blocker,H., Ramser,J., Beck,A., Klages,S.,  
Hennig,S., Riesselmann,L., Dagand,E., Haaf,T., Wehrmeyer,S.,  
Borzym,K., Gardiner,K., Nizetic,D., Francis,F., Lehrach,H.,  
Reinhardt,R. and Yaspo,M.L.

TITLE The DNA sequence of human chromosome 21

JOURNAL Nature 405 (6784), 311-319 (2000)

MEDLINE [20289799](#)

PUBMED [10830953](#)

REFERENCE 3 (residues 1 to 2012)

AUTHORS Agarwala,K.L., Nakamura,S., Tsutsumi,Y. and Yamakawa,K.

TITLE Down syndrome cell adhesion molecule DSCAM mediates homophilic  
intercellular adhesion

JOURNAL Brain Res. Mol. Brain Res. 79 (1-2), 118-126 (2000)

MEDLINE [20384934](#)

PUBMED [10925149](#)

COMMENT PROVISIONAL REFSEQ: This record has not yet been subject to final  
NCBI review. The reference sequence was derived from [AF217525.1](#).  
On Apr 10, 2002 this sequence version replaced [gi:14277122](#).

FEATURES Location/Qualifiers

source 1..2012



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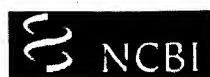
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661 lmhngnytc arneaaaveh qsqlivrpp kfvvqprdq giygkaviln csaegypvpt  
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841 evgeevistl qilptvreds gffschains ygedrgiiql tvqepdppe ieikdvkart  
901 itlrwtmgfd gnsptigydi ecknksdswd saqrtdkvsp qlnsatiidi hpsstysirm  
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1021 qigyreystg gnfqfniisv dtsgdsevyt ldnlkftqy glvvqacnra gtgppsgeii  
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Revised: October 24, 2001.

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PubMed	Nucleotide	Protein	Genome	Structure	PopSet	Taxonomy	OMIM	Books
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☐ 1: AAC17967. Down syndrome  
cel...[gi:3169768]

BLink, Nucleotide, OMIM, Related Sequences, PubMed,  
Taxonomy, LinkOut

LOCUS AAC17967 1571 aa linear PRI 30-MAR-2001  
DEFINITION Down syndrome cell adhesion molecule [Homo sapiens].  
ACCESSION AAC17967  
PID g3169768  
VERSION AAC17967.1 GI:3169768  
DBSOURCE locus AF023450 accession AF023450.1  
KEYWORDS .  
SOURCE human.  
ORGANISM Homo sapiens  
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;  
Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.  
REFERENCE 1 (residues 1 to 1571)  
AUTHORS Yamakawa,K., Huot,Y.K., Haendelt,M.A., Hubert,R., Chen,X.N.,  
Lyons,G.E. and Korenberg,J.R.  
TITLE DSCAM: a novel member of the immunoglobulin superfamily maps in a  
Down syndrome region and is involved in the development of the  
nervous system  
JOURNAL Hum. Mol. Genet. 7 (2), 227-237 (1998)  
MEDLINE 98087574  
PUBMED 9426258  
REFERENCE 2 (residues 1 to 1571)  
AUTHORS Yamakawa,K., Huo,Y.-K., Haendel,M.A., Hubert,R., Chen,X.-N.,  
Lyons,G.E. and Korenberg,J.R.  
TITLE Direct Submission  
JOURNAL Submitted (08-SEP-1997) Medical Genetics, Cedars-Sinai Research  
Institute, 110 George Burns Road, Davis Building, Suite 2005, Los  
Angeles, CA 90048-1869, USA  
COMMENT Method: conceptual translation supplied by author.  
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/tissue\_type="brain"  
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## ORIGIN

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721 ivwkftskgag vqqfqpialn griqvlsgs llikhvveed sgpylckvsn dvgadvsksm
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//

Revised: October 24, 2001.

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PubMed	Nucleotide	Protein	Genome	Structure	PopSet	Taxonomy	OMIM	Books
Search		Protein	for		Go		Clear	
Limits		Preview/Index		History		Clipboard		Details
Display	default	Save	Text		Add to Clipboard			

☐ 1: O60469. Down syndrome cel...[gi:12643619] [BLink](#), [OMIM](#), [Related Sequences](#), [PubMed](#), [Taxonomy](#), [LinkOut](#)

LOCUS DSCA\_HUMAN 2012 aa linear PRI 01-MAR-2002  
DEFINITION Down syndrome cell adhesion molecule precursor (CHD2).  
ACCESSION O60469  
PID g12643619  
VERSION O60469 GI:12643619  
DBSOURCE swissprot: locus DSCA\_HUMAN, accession O60469;  
class: standard.  
extra accessions:O60468,created: Oct 16, 2001.  
sequence updated: Oct 16, 2001.  
annotation updated: Mar 1, 2002.  
xrefs: gi: gi: 3169767, gi: gi: 3169768, gi: gi: 3169765, gi: gi:  
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7717375  
xrefs (non-sequence databases): MIM 602523, InterPro IPR003961,  
InterPro IPR003962, InterPro IPR003006, InterPro IPR003598,  
InterPro IPR003600, Pfam PF00041, Pfam PF00047, PRINTS PR00014,  
SMART SM00060, SMART SM00410, SMART SM00408  
KEYWORDS Immunoglobulin domain; Glycoprotein; Signal; Cell adhesion; Repeat;  
Transmembrane; Alternative splicing.  
SOURCE human.  
ORGANISM Homo sapiens  
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;  
Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.  
REFERENCE 1 (residues 1 to 2012)  
AUTHORS Yamakawa,K., Huot,Y.K., Haendelt,M.A., Hubert,R., Chen,X.N.,  
Lyons,G.E. and Korenberg,J.R.  
TITLE DSCAM: a novel member of the immunoglobulin superfamily maps in a  
Down syndrome region and is involved in the development of the  
nervous system  
JOURNAL Hum. Mol. Genet. 7 (2), 227-237 (1998)  
MEDLINE 98087574  
REMARK SEQUENCE FROM N.A., AND ALTERNATIVE SPLICING.  
TISSUE=Brain  
REFERENCE 2 (residues 1 to 2012)  
AUTHORS Agarwala,K.L., Nakamura,S., Tsutsumi,Y. and Yamakawa,K.  
TITLE Down syndrome cell adhesion molecule DSCAM mediates homophilic  
intercellular adhesion  
JOURNAL Brain Res. Mol. Brain Res. 79 (1-2), 118-126 (2000)  
MEDLINE 20384934  
REMARK SEQUENCE FROM N.A., AND FUNCTION.  
REFERENCE 3 (residues 1 to 2012)  
AUTHORS Hattori,M., Fujiyama,A., Taylor,T.D., Watanabe,H., Yada,T.,  
Park,H.-S., Toyoda,A., Ishii,K., Totoki,Y., Choi,D.-K., Soeda,E.,  
Ohki,M., Takagi,T., Sakaki,Y., Taudien,S., Blechschmidt,K.,  
Polley,A., Menzel,U., Delabar,J., Kumpf,K., Lehmann,R.,  
Patterson,D., Reichwald,K., Rump,A., Schillhabel,M., Schudy,A.,  
Zimmermann,W., Rosenthal,A., Kudoh,J., Shibuya,K., Kawasaki,K.,  
Asakawa,S., Shintani,A., Sasaki,T., Nagamine,K., Mitsuyama,S.,  
Antonarakis,S.E., Minoshima,S., Shimizu,N., Nordsiek,G.,  
Hornischer,K., Brandt,P., Scharfe,M., Schoen,O., Desario,A.,

Reichelt, J., Kauer, G., Bloecker, H., Ramser, J., Beck, A., Klages, S., Hennig, S., Riesselmann, L., Dagand, E., Wehrmeyer, S., Borzym, K., Gardiner, K., Nizetic, D., Francis, F., Lehrach, H., Reinhardt, R. and Yaspo, M.-L.

TITLE The DNA sequence of human chromosome 21  
JOURNAL Nature 405 (6784), 311-319 (2000)  
MEDLINE 20289799  
REMARK SEQUENCE FROM N.A.  
COMMENT

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[FUNCTION] CELL ADHESION MOLECULE THAT CAN MEDIATE CATION-INDEPENDENT HOMOPHILIC BINDING ACTIVITY. COULD BE INVOLVED IN NERVOUS SYSTEM DEVELOPMENT.

[SUBCELLULAR LOCATION] TYPE I MEMBRANE PROTEIN (PROBABLE). THE SHORT ISOFORM MAY BE SECRETED.

[ALTERNATIVE PRODUCTS] 2 ISOFORMS; A LONG FORM/CHD2-52 (SHOWN HERE) AND A SHORT FORM/CHD2-42; ARE PRODUCED BY ALTERNATIVE SPLICING.

[TISSUE SPECIFICITY] PRIMARILY EXPRESSED IN BRAIN.

[SIMILARITY] BELONGS TO THE IMMUNOGLOBULIN SUPERFAMILY.

[SIMILARITY] CONTAINS 10 IMMUNOGLOBULIN-LIKE C2-TYPE DOMAINS.

[SIMILARITY] CONTAINS 6 FIBRONECTIN TYPE III-LIKE DOMAINS.

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Protein	1..2012 /product="Down syndrome cell adhesion molecule precursor"
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Region	18..1595 /region_name="Domain" /note="EXTRACELLULAR (POTENTIAL)."
Region	18..2012 /region_name="Mature chain" /note="DOWN SYNDROME CELL ADHESION MOLECULE."
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Bond	bond(145,197) /bond_type="disulfide" /note="BY SIMILARITY."
Region	239..300 /region_name="Domain" /note="IG-LIKE C2-TYPE DOMAIN 3."
Bond	bond(246,293) /bond_type="disulfide"



/note="BY SIMILARITY."  
Region 328..392  
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Region 610..676  
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Bond bond(617,669)  
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Site 658  
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Site 666  
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Bond bond(711,766)  
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Site 748  
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Region 1088..1177  
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Site 1271  
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## ORIGIN

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Revised: October 24, 2001.

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☐ 1: AAC17966. Down syndrome  
cel...[gi:3169766]

BLink, Nucleotide, OMIM, Related Sequences, PubMed,  
Taxonomy, LinkOut

LOCUS AAC17966 1896 aa linear PRI 30-MAR-2001  
 DEFINITION Down syndrome cell adhesion molecule [Homo sapiens].  
 ACCESSION AAC17966  
 PID g3169766  
 VERSION AAC17966.1 GI:3169766  
 DBSOURCE locus AF023449 accession [AF023449.1](#)  
 KEYWORDS .  
 SOURCE human.  
 ORGANISM Homo sapiens  
 Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;  
 Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.  
 REFERENCE 1 (residues 1 to 1896)  
 AUTHORS Yamakawa,K., Huot,Y.K., Haendelt,M.A., Hubert,R., Chen,X.N.,  
 Lyons,G.E. and Korenberg,J.R.  
 TITLE DSCAM: a novel member of the immunoglobulin superfamily maps in a  
 Down syndrome region and is involved in the development of the  
 nervous system  
 JOURNAL Hum. Mol. Genet. 7 (2), 227-237 (1998)  
 MEDLINE 98087574  
 PUBMED 9426258  
 REFERENCE 2 (residues 1 to 1896)  
 AUTHORS Yamakawa,K., Huo,Y.-K., Haendel,M.A., Hubert,R., Chen,X.-N.,  
 Lyons,G.E. and Korenberg,J.R.  
 TITLE Direct Submission  
 JOURNAL Submitted (08-SEP-1997) Medical Genetics, Cedars-Sinai Research  
 Institute, 110 George Burns Road, Davis Building, Suite 2005, Los  
 Angeles, CA 90048-1869, USA  
 COMMENT Method: conceptual translation.  
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 CDS 1..1896  
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 /note="member of immunoglobulin superfamily; involved in  
 nervous system development"  
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 121 tmrgnvavfk ciipssveay itvvswekdt vslvsgsrfl itstgalyik dvqnedglyn  
 181 yrcitrhryt getrqnsar lfvspansa psildgfdhr kamagqrvel pckalghpep  
 241 dyrwlkdnmp lelsgrfqkt vtgllienir psdsgsyvce vsnrygtakv igrlyvkqpl

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721 qpialngriq vlsngsllik hvveedsgyy lckvsndvga dvsksmylv kipamitsyp
781 nttlatggqk kemsctahge kpiivrweke driinpemar ylvstkevge evistlqilp
841 tvredsgffs chainsyged rgiiqltvqe pdppeieik dvkartitlr wtmgfdgns
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Revised: October 24, 2001.

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